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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,699	10/02/2003	David Bar-Or	4172-85	2007

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/679,699	BAR-OR ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *2,4,5,9-12,20-23 and 33-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6-8,13-19 and 24-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-46* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/11/04; 8/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS: 6/6/06*.

DETAILED ACTION

Election/Restrictions

Applicant's elections without traverse of Group I claims 1-32, and the species of: N-acetyl-Ala-Ser DKP (NAS-DKP), myelin basic protein and multiple sclerosis, in the reply filed on 17 August 2006 are acknowledged.

Claims 2, 4, 5, 9-12, 20-23 and 33-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected subject matter, there being no allowable generic or linking claim.

Claims 1, 3, 6-8, 13-19 and 24-32 are under examination in the instant office action to the extent that the claims read on the elected species.

Information Disclosure Statements

Signed and initialed copies of the IDS papers filed 11 June 2004, 09 August 2005 and 06 June 2006 are enclosed in this action.

Specification

The disclosure is objected to because of the following informalities: P.19, line 9 contains the typo, "DA-KDP".

Appropriate correction is required.

Claim Objections

Claims 24-32 are objected to because of the following informalities: Said claims depend from non-elected base claims, i.e., claims 20 and 22. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6-8, 13-19 and 24-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are drawn to a method for diagnosing or monitoring a disease or condition comprising the steps of: (a) obtaining a biological sample from a patient to be

diagnosed or monitored; (b) determining the quantity of a target marker in said biological sample, wherein said target marker is: (i) a truncated disease-associated protein lacking its two N-terminal amino acids, wherein said truncated disease-associated protein is not human serum albumin; (ii) a truncated disease-associated protein lacking its two C-terminal amino acids; (iii) a truncated disease-associated protein lacking its two N-terminal amino acids and its two C-terminal amino acids; (iv) a diketopiperazine (DKP) comprising the two N-terminal amino acids of a disease-associated protein; or (v) a DKP comprising the two C-terminal amino acids of a disease- associated protein; or (vi) two or more target markers selected from those listed in (i) through (v) above; provided that when only a single DKP is used as the marker, it will not be His-Pro DKP; and (c) determining if the quantity(ties) of said target marker(s) in said biological sample is(are) indicative of the presence, absence or status of the disease or condition.

Applicants' examples on pp.23-30 of the specification teach the measurement of diketopiperazines in blood samples taken from pregnant mothers with preeclampsia and HELLP syndrome, from multiple sclerosis patients, and from Alzheimer's patients. Applicants measured potential markers with liquid chromatography followed by mass spectrometry.

There were twelve patients in the pregnant mother experimental group and 5 patients in the pregnant mother control group. Results from one patient in the pregnant mother experimental group are presented in figures 2 and 4, which reveal the presence

of GL-DKP (glycine-leucine DKP derived from β–human chorionic gonadotropin or βHCG) and AP-DKP (alanine-proline DKP derived from fetal erythropoietin).

There were 13 patients in the active MS experimental group, 16 patients in the non-active MS group and 8 patients in the control group. Standards of DA-DKP and EA-DKP only were run with each set of data, and there were no calibrants for some of the markers outlined below (although the sensitivity of the instrument was assumed to be linear across the spectrum as derived from the linearity of the detection of DA-DKP and EA-DKP). After choosing a set of 10 putative masses for analysis, the data were analyzed with a clustering toolset, and "trial and error analysis" revealed that 2 masses of 185 and 199 appearing early in the runs had some power to separate the data into two groups, one of which was designated active MS and the other was designated non-active MS and normals. Further, in a subset of MS and normal patients, the settings were optimized to achieve good separation between active MS and all other diagnoses. It is taught that the cluster of data points which corresponded to the mass of 185 (samples from controls and non-active MS patients) was identified as DA-DKP (Asp-Ala DKP), and the cluster of data points which corresponded to the mass of 199 was identified as NAS-DKP (samples from active MS patients). DA-DKP is taught to be the degradation product of beta amyloid and NAS-DKP is taught to be the degradation product of myelin basic protein. Other potential markers are taught, e.g., markers labeled "175 @8.5 minutes" and "145 @12.7 minutes," and the former appeared to be deficient in all MS patients but unusually high for Alzheimer's disease patients. It is

noted that no data referring to the selection and number of Alzheimer's disease patients included in any study is disclosed.

Applicants present data obtained from patients pre-selected for having preeclampsia and HELLP syndrome or MS (active or non-active). In support of the method of detecting placental ischemia, Applicants present data from one patient. Accordingly, this one sample would not necessarily be predictive of all patients with placental ischemia. Further, Applicants' data are correlative only; there is no true nexus established between Applicants' data and diagnosis or monitoring of any disease or condition.

Applicants' claims encompass diagnosing any disease or condition with any truncated disease associated protein or any disease associated DKP (other than His-Pro DKP). Accordingly, if one considers only a subset of the disease states encompassed by the claims, e.g. neurodegenerative disorders, it is well known in the art that said disorders have different symptoms, pathologies, and etiologies. For example, multiple sclerosis is an autoimmune disease characterized by multiple regions of demyelination and inflammation along axonal pathways and an upregulation of inflammatory factors and cells in the cerebrospinal fluid (Purves *et al.* Neuroscience second edition, p. 75). Parkinson's disease is characterized by defects in motor function, e.g. resting tremor, rigidity of extremities and neck, shortened steps with minimal arm swinging, and stooped posture, due to the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (p. 403). Huntington's disease is characterized by the gradual onset of defects in motor behavior, cognition,

and movement, e.g. mood alterations, dementia, memory deficits, and rapid, jerky motions with no clear purpose resulting from a profound and selective atrophy of the caudate, putamen, and some degeneration of the frontal and temporal cortices (p. 400). Further, amyotrophic lateral sclerosis is characterized by the slow but inevitable degeneration of α motor neurons in the spinal cord ventral horns and brainstem and neurons in the motor cortex leading to eventual paralysis and death (p. 367). Since these disorders are fundamentally different in terms of pathology and etiology as outlined above, an assay method that attempts to detect all of them would be unpredictable. Given the highly unpredictable nature of diagnosing or detecting any disease or disorder associated with any DKP or any truncated disease associated protein (missing the two N-terminal or C-terminal amino acid residues or both), one of skill in the art could not be reasonably assured that the disclosed invention would be indicative of said diseases or disorders. One of skill in the art may be able to detect portions of disease associated proteins; however the claimed method reveals nothing regarding the potential source and or cause of the truncated proteins or other causative factors that may be involved in any particular disease state.

Additionally, Andreasen et al. (Arch. Neurol. Jun; 56(6): pp. 673-80, 1999) state that even today the diagnosis of Alzheimer's is definite only with an autopsy examination (p. 673, line 7-9) and that there is a pressing need for biochemical diagnostic markers of AD (lines 15-16). Andreasen et al. teach a detailed analysis for evaluating β-amyloid $_{(1\text{-}42)}$ in CSF as a diagnostic for Alzheimer's disease. Without such

rigorous scientifically based analysis, for example, one could not be assured of the predictive or diagnostic nature of the claimed assay methods.

Also, Bielekova et al. (Brain. 2004 Jul;127(Pt 7):1463-78. Epub 2004 Jun 4) teaches that diagnosis of MS is unpredictable since "multiple sclerosis is a complex disease, as several pathophysiological processes (including inflammation, demyelination, axonal damage and repair mechanisms) participate in the disease process. Furthermore, as new pathological evidence reveals, these processes are not uniformly represented across patient populations but can selectively predominate in individual patients, thus contributing to the heterogeneity in phenotypic expression of the disease, its prognosis and response to therapies" (Abstract). Bielekova et al. defines the term biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" and defines a surrogate endpoint as "a biomarker that is intended to serve as a substitute for a clinically meaningful endpoint and is expected to predict the effect of a therapeutic intervention" (pp.1463-4). Further, the reference teaches that there are two conditions that ensure the surrogacy of a biomarker: 1) a strong and significant correlation between the biomarker and a clinical endpoint and 2) the biomarker must fully capture the net effect of the treatment on the true clinical endpoint. The reference also teaches that "this is virtually impossible, because some of the adverse effects of therapy may be completely unrelated to the pathophysiology of the disease and yet may negatively influence the clinical endpoint...In multiple sclerosis, the situation is further complicated by the fact

that the disease pathophysiology is complex and the applied therapy may positively influence only one of the contributing processes (e.g. effect of immunosuppressive therapies on inflammation) and have no effect, or potentially have even negative influence on others" (p.1464). Thus, even with further clinical measures, for example, one could not be assured of the predictive or diagnostic nature of the claimed assay methods for initial diagnosis and/or monitoring of MS.

In addition, the art accepted diagnosis for Parkinson's disease is difficult and may be mimicked by other diseases (see Michell et al. Brain. Aug; 127: pp.1693-1705, 2004 for review). Michell et al. teaches that "the key pathology is in the brainstem, hidden from direct study during life, and this coupled to a fluctuating clinical syndrome over time, makes it difficult to monitor in an unbiased and objective manner" (p. 1693, paragraph 2). Michell et al. also teaches " biomarkers aim to improve our data collection about the clinical and pathological parameters of disease which is complicated in Parkinson's disease by a rather poor correlation between the underlying pathology and the subsequent clinical phenotype" (paragraph 3). Further, it is taught, "no biomarker is likely to fulfill all of these functions [help diagnose symptomatic and presymptomatic disease]" (see abstract). Thus, given the art-accepted nature of diagnosing or detecting Parkinson's disease, one of skill in the art could not be reasonably assured that the claimed invention would be indicative of said disease.

Regarding conditions other than neurodegenerative disorders, the art teaches that identifying cancer (for example) from bodily fluids, such as blood, is unpredictable. Relevant art regarding stomach cancer teaches that it is often difficult to find an

antigens or gene transcripts that are expressed only by tumor cells and not by surrounding cells, because those expressed by the primary tumor cell may have been downregulated or lost (Vogel et al. Virchows Arch 439:109-117, 2001). Vogel et al. teaches that it is assumed that disseminated tumor cells of non-haematopoietic origin normally do not circulate in the peripheral blood (p.110, paragraph 7).

Furthermore, Skates et al. (Clin Cancer Res 10:6296S-301S, 2004) teaches that even if a biomarker for renal cell carcinoma was extremely sensitive and had an extremely high specificity, the positive predictive value would still be low and "achieving such an exacting combination of sensitivity and specificity is unlikely for a blood test" (p.6296s, para.4). Skates et al. also teaches that further testing i.e. more expensive imaging tests, would be needed to validate the findings of a blood test (para.4).

In addition, Bunn (J Clin Oncol 21(21): 3891-3, 2003) teaches that studies of serum protein markers for lung cancer failed to produce sufficient sensitivity or specificity for routine use (p.3891, para.1). Bunn also teaches that although some studies have shown that DNA markers for cancer are present in the serum, "much remains to be done before these tests become standard (para.2). Accordingly, Bunn presents a diversity of findings between studies evaluating serum plasma markers in lung cancer patients (p.3892, Table 1) reflecting the unpredictability of such an assay. Bunn concludes, "for lung cancer, much needs to be done in validation, and much larger series must be completed before these tests are ready for prime time" (p.3893). Further, Shaw et al. (Clin Cancer Res. 11(13 Pt 2): 4999s-5003s, 2005) teaches, "no reliable circulating biomarkers of lung cancer have been identified that allow early

diagnosis" (Abstract). Shaw et al. also teaches that although mouse models of lung cancer show some promise, "before any biomarkers can enter into clinical practice, they will need to be validated in patient samples" and in clinical trials (5003s).

Furthermore, the prior art discussed *supra* does not address bodily fluid samples other than blood or serum. For example, while it may be possible to detect bladder cancer from urine samples and lung cancer from sputum, it is unclear how stomach cancer would be detected from urine. Similarly, how would the artisan detect breast cancer from saliva? Such details are missing from Applicants' disclosure.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the large quantity of experimentation necessary to establish a nexus between the claimed assay methods reciting truncated disease associated proteins and the diagnosis and/or monitoring of any disease and/or condition, given the lack of direction/guidance presented in the specification, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the claimed methods, and the breadth of the claims which encompass methods of diagnosing or monitoring any disease in any bodily fluid or tissue sample, undue experimentation would be required of the skilled artisan to practice the claimed invention.

Claims 1, 3, 6-8, 13-19 and 24-32 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method for diagnosing or monitoring a disease or condition comprising the steps of: (a) obtaining a biological sample from a patient to be diagnosed or monitored; (b) determining the quantity of a target marker in said biological sample, wherein said target marker is: (i) a truncated disease-associated protein lacking its two N-terminal amino acids, wherein said truncated disease-associated protein is not human serum albumin; (ii) a truncated disease-associated protein lacking its two C-terminal amino acids; (iii) a truncated disease-associated protein lacking its two N-terminal amino acids and its two C-terminal amino acids; (iv) a diketopiperazine (DKP) comprising the two N-terminal amino acids of a disease-associated protein; or (v) a DKP comprising the two C-terminal amino acids of a disease- associated protein; or (vi) two or more target markers selected from those listed in (i) through (v) above; provided that when only a single DKP is used as the marker, it will not be His-Pro DKP; and (c) determining if the quantity(ties) of said target marker(s) in said biological sample is(are) indicative of the presence, absence or status of the disease or condition.

These are genus claims because they are directed to a plurality of undisclosed amino acid molecules, i.e., the target markers (truncated disease associated proteins

and diketopiperazines) and the binding partners specific for the target markers. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural features of the genus of amino acid sequences such that they would be functional in the claimed methods. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the amino class are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, any truncated disease associated protein, any DKP except His-Pro DKP or any binding partner is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number

of species to describe the genus. Thus, Applicants are not in possession of the claimed genus.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached on Monday through Friday from 9AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1649
28 August 2006

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